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ORIGINAL ARTICLE

Gender-specific risks for incident cancer in patients with different heart failure phenotypes

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Abstract

Background There is conflicting evidence regarding whether heart failure (HF) increases the risk of developing cancer.
Objective This study aimed to assess the association between HF and incident cancer, considering gender differences and HF phenotypes.
Methods This retrospective study was conducted on data of adult individuals, free of cancer at baseline, from the First Affiliated Hospital of Wenzhou Medical University between January 2009 and February 2023. The patients with HF were categorized as HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF). The primary outcome was incident cancer, including obesity-related, tobacco-related, lung, colorectal and breast cancers.
Results Of 33 033 individuals enrolled, 16 722 were diagnosed with HF, including 10 086 (60.3%) with HFpEF and 6636 (39.7%) with HFrEF. During a median follow-up period of 4.6 years (inter-quartile range: 2.6–7.3), incident cancer was diagnosed in 10.5% (1707 patients) of the non-HF group and 15.1% (2533 individuals) of the HF group. After adjusting for potential confounding factors, patients with HF had a 58% increased risk of cancer than those without HF [adjusted hazard ratio (HR) 1.58, 95% confidence interval (CI) 1.48–1.69, $P < 0.001$]. This risk was consistent across genders (female: adjusted HR 1.95, 95% CI 1.74–2.18, $P < 0.001$; male: adjusted HR 1.41, 95% CI 1.30–1.54, $P < 0.001$) and HF phenotypes (HFpEF: adjusted HR 1.69, 95% CI 1.57–1.81, $P < 0.001$; HFrEF: adjusted HR 1.32, 95% CI 1.20–1.46, $P < 0.001$).
Conclusions Both HFpEF and HFrEF are associated with an increased risk of incident cancer. This correlation maintains its validity across genders.

Keywords cardio-oncology; cancer; heart failure; heart failure with reduced ejection fraction; heart failure with preserved ejection fraction; prognosis

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Introduction

Cancer and heart failure (HF) are among the foremost contributors to global morbidity and mortality, collectively imposing a significant disease burden worldwide.[1–3] They often coexist, suggesting shared risk factors and underlying mechanisms.[4–7] As cancer survival rates have improved, cardiovascular disease (CVD) has become the most common non-cancer cause of death among cancer patients, partly due to complications from anti-cancer treatments.[8,9] Conversely, with advances in HF treatment, cancer now ranks as the primary cause of non-CVD mortality in patients with chronic HF.[8–10]

Recent interest has focused on understanding incident cancer risk among patients with HF. Studies from various global settings, including population-based cohorts in the USA,[11,12] national registries in Denmark and Korea[13,14] and observational studies in Danish,[15] Germany[16] and Italy,[17] have explored this relationship. However, findings from the Physi-

cians' Health Studies (PHS) and the Women's Health Initiative (WHI) indicate variability in these associations, particularly concerning differences related to HF phenotype and gender.[18] Subsequently, Leedy et al. analysed data from the WHI study, comprising three clinical trials and an observational study involving post-menopausal women, revealing that HF is linked to an increased risk of cancer, particularly lung cancer.[19] They noted a significant association among patients with HF with preserved ejection fraction (HFpEF) but not among those with HF with reduced ejection fraction (HFrEF). They suggested that inconsistent earlier findings may stem from underrepresentation of women and inadequate consideration of HF phenotype in prior studies. However, their study focused exclusively on women over 50 years old, limiting generalizability to younger women and the broader population. While causality cannot be definitively determined in observational studies, these results underscore the need for further investigation.[20] Moreover, most of the aforementioned studies primarily included White/Caucasian populations.[21]

The present study aims to explore the potential association between HF phenotype and cancer incidence, taking into account gender differences, within a Chinese population.

Methods

Study design

This retrospective study enrolled consecutive adult individuals, both with and without HF, who were hospitalized or attended outpatient clinics, including those specialized in HF, at the First Affiliated Hospital of Wenzhou Medical University from January 2009 to February 2023. Eligible patients underwent comprehensive echocardiographic assessment with available data on left ventricular ejection fraction (LVEF). Exclusions were made for individuals with a history of cancer, newly diagnosed cancer within 1 year after enrolment or follow-up duration of less than three years (unless cancer was diagnosed earlier). Patient data, encompassing demographic details, medical histories, medication records, specifics of echocardiographic evaluations and follow-up information, were gathered from electronic medical records. This research adhered to the principles outlined in the Declaration of Helsinki and received approval from the ethics committee at the First Affiliated Hospital of Wenzhou Medical University (Approval No. KY2023-R267). Because the study was retrospective, individual patient consent was waived. The checklist of the study is provided in the supporting information (Data S1).

Definition

The primary outcome was the first incident of cancer. All incident cancers were documented and reviewed centrally through the electronic medical record system including inpatients and outpatients. We developed categories based on cancer diagnoses to investigate our hypotheses around shared risk factors.[17] These categories include obesity-related and tobacco-related cancers. Obesity-related cancers were those that the International Agency for Research on Cancer (IARC) had identified as having a connection to obesity, such as oesophageal, gastric, colorectal, liver, post-menopausal breast, pancreatic, ovarian, kidney, uterine, thyroid or multiple myeloma.[22] Tobacco-related cancers were those that IARC had linked to tobacco use, such as lung, stomach, pancreas, liver, kidney, oral, oropharynx, nasopharynx, nasal, hypopharynx, larynx, oesophageal, bladder, ureter or cervix.[23] HF was documented from review of hospitalization records. Each patient with HF should have at least one of the following: (1) history of hospitalization for $\geq$24 h with a primary diagnosis of HF, (2) LVEF $\leq$ 40% and (3) clinical diagnosis of HF in HF outpatient clinic based on symptoms and/or signs and elevated B-type natriuretic peptide levels. HF was distinguished as HFpEF (LVEF $\geq$ 50%) or HFrEF (LVEF $<$ 50%). We collected clinical follow-up data until April 2023 from inpatient and outpatient medical records to analyse clinical outcomes. The duration of the follow-up period was determined by the time between the diagnosis of HF and either the final clinical follow-up or time-to-event endpoints, whichever came first.

Statistical analysis

We presented the mean ± standard deviation (*SD*) for normally distributed continuous variables and the median with inter-quartile range (IQR) for non-normally distributed continuous variables. Categorical variables were expressed as the number (%) of patients. To compare groups, we used the Student *t*-test (for normally distributed continuous variables), Mann–Whitney *U* test (for non-normally distributed continuous variables), and Chi-squared test (for categorical variables). The incidence rates (cases/1000 person-years) and 95% confidence intervals (CIs) for any cancer were also calculated, comparing participants with HF vs. no HF, stratified by HF phenotype at enrolment. Furthermore, we developed a Cox proportional hazards model and calculated hazard ratios (HR) and 95% CI to evaluate the impact of HF on incident cancer during the follow-up period. Variables for inclusion in the multivariable analysis were decided a priori based on known confounders, including adjusted for age, sex, body mass index, current smoking, current drinking, hypertension, diabetes mellitus, myocardial infarction, atrial fibrillation, previous stroke and chronic kidney disease. We conducted another analysis on HF phenotype, classified HF as HFpEF or HFrEF and compared them to those without HF (reference group). We also calculated event-free survival curves using the Kaplan–Meier method and compared the differences

among various HF phenotypes with the log-rank test. Distinct models were employed to analyse multiple types of cancer, including any cancer, cancers related to obesity-related, tobacco-related, lung, colorectal and breast cancers. A systematic review was conducted to comprehensively evaluate the potential links between new cases of cancer and HF. Initially, original studies that reported on the association between incident cancer and HF, with or without HF subtypes, were included. Additionally, the findings from the current study were also taken into account. HRs were extracted from fully adjusted models and combined using generic inverse variance and random-effects models. Furthermore, the impact of our results and other individual studies on the combined outcome was assessed by removing one study at a time to check for undue influence. We considered a significance level of $P < 0.05$ (two-tailed) statistically significant. The statistical analyses were performed with IBM SPSS software (version 26.0) and R software (version 4.0.4).

Results

Baseline characteristics

After screening potential participants against the study's inclusion criteria, a final sample of 33 033 individuals was included in the analysis. The characteristics of the participants stratified by non-HF and total HF groups are presented in *Table* 1. The patient population comprised 38.7% females; the average age at enrolment was 64.2 ± 12.4 years. The HF cohort included individuals older than non-HF (65.5 ± 12.9 vs. 62.9 ± 11.6), more likely to identify as female, and more likely to have a history of diabetes, myocardial infarction and chronic kidney disease. Among the HF cohort (16 722), HFpEF and HFrEF accounted for 10 086 (60.3%) and 6636 (39.7%) participants, respectively. In a cohort of 16 722 individuals with HF, 60.3% (10 086 participants) were diagnosed with HFpEF and 39.7% (6636 participants) with HFrEF. The causes of HF varied, including 3123 (18.7%) with dilated cardiomyopathy, 4895 (29.3%) with hypertensive heart disease, 867 (5.2%) with hypertrophic cardiomyopathy, 2182 (13.0%) with valvular heart disease, 3876 (23.2%) with ischemic heart disease and 1779 (10.6%) with other or unknown causes. Other baseline characteristics by HFpEF and HFrEF are presented in *Table* 2.

Association between HF and incidence of cancer stratified by non-HF, HFpEF and HFrEF

Over a study period of 4.6 years (IQR: 2.6–7.3 years), 15.1% (2533 individuals) in the HF group were diagnosed with cancer with an average age of 71.9 ± 13.8 years, while 10.5%

Table 1 Baseline characteristics of participants stratified by non-HF and total HF.

	Total cohort (n = 33 033)	Non-HF (n = 16 311)	Total HF (n = 16 722)	P value
Age, years	64.2 ± 12.4	62.9 ± 11.6	65.5 ± 12.9	<0.001
Male	20 238 (61.3%)	11 049 (67.7%)	9 189 (55.0%)	<0.001
BMI, kg/m^2	24.1 ± 3.1	24.3 ± 3.0	23.9 ± 3.3	<0.001
Current smoking	12 733 (38.5%)	6922 (42.4%)	5811 (34.8%)	<0.001
Current drinking	9863 (29.9%)	5476 (33.6%)	4387 (26.2%)	<0.001
Follow-up, years	4.9 ± 3.0	4.9 ± 2.9	4.9 ± 3.0	0.645
Comorbidities				
Hypertension	15 766 (47.7%)	7991 (49.0%)	7775 (46.5%)	<0.001
Diabetes mellitus	6465 (19.6%)	3056 (18.7%)	3409 (20.4%)	<0.001
Myocardial infarction	3369 (10.2%)	1202 (7.4%)	2167 (13.0%)	<0.001
Atrial fibrillation	2686 (8.1%)	803 (4.9%)	1883 (11.3%)	<0.001
Previous stroke	2549 (7.7%)	1328 (8.1%)	1221 (7.3%)	0.005
Chronic kidney disease[a]	5804 (17.6%)	1987 (12.2%)	3817 (22.8%)	<0.001
Baseline echo				
LVEF, %	59.6 ± 12.2	65.0 ± 6.5	54.4 ± 14.0	<0.001
LAD, mm	42.2 ± 7.1	40.4 ± 5.6	44.0 ± 7.9	<0.001
LVED, mm	50.8 ± 7.2	48.9 ± 5.1	52.6 ± 8.4	<0.001
LVSD, mm	36.4 ± 8.5	33.9 ± 6.4	38.9 ± 9.6	<0.001
Medicine, n (%)				
Loop diuretic	9372 (28.4%)	1134 (7.0%)	8238 (49.3%)	<0.001
MRA	6493 (19.7%)	615 (3.8%)	5878 (35.2%)	<0.001
CCB	15 180 (46.0%)	7518 (46.1%)	7662 (45.8%)	0.624
Beta-blocker	17 367 (52.6%)	7736 (47.4%)	9631 (57.6%)	<0.001
ACEI/ARB/ARNI	18 175 (55.0%)	7969 (48.9%)	10 206 (61.0%)	<0.001
Statin	22 968 (69.5%)	11 697 (71.7%)	11 271 (67.4%)	<0.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; CCB, calcium channel blockers; HF, heart failure; LAD, left atrial diameter; LVDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVSD, left ventricular end-systolic diameter; MRA, mineralocorticoid receptor antagonist.
[a]Estimated glomerular filtration rate <60 mL/min/1.73 m^2.

Table 2 Baseline characteristics of participants with HF stratified by HFrEF and HFpEF.

	HFrEF (n = 6636)	HFpEF (n = 10 086)	P value
Age, years	64.0 ± 13.8	66.5 ± 12.2	<0.001
Male	4856 (73.2%)	4333 (43.0%)	<0.001
BMI, kg/m^2	23.6 ± 3.2	24.0 ± 3.4	<0.001
Current smoking	3063 (46.2%)	2748 (27.2%)	<0.001
Current drinking	2098 (31.6%)	2289 (22.7%)	<0.001
Follow-up, years	4.4 ± 2.8	5.2 ± 3.1	<0.001
Comorbidities			
Hypertension	2579 (38.9%)	5196 (51.5%)	<0.001
Diabetes mellitus	1117 (16.8%)	2292 (22.7%)	<0.001
Myocardial infarction	1622 (24.4%)	545 (5.4%)	<0.001
Atrial fibrillation	738 (11.1%)	1145 (11.4%)	0.662
Previous stroke	349 (5.3%)	872 (8.6%)	<0.001
Chronic kidney disease[a]	1698 (25.6%)	2119 (21.0%)	<0.001
Baseline echo			
LVEF, %	39.6 ± 7.7	64.2 ± 6.8	<0.001
LAD, mm	45.1 ± 7.5	43.3 ± 8.1	<0.001
LVEDD, mm	57.5 ± 8.9	49.4 ± 6.2	<0.001
LVSDD, mm	45.2 ± 9.1	34.9 ± 7.7	<0.001
Medicine, n (%)			
Loop diuretic	4278 (64.5%)	3960 (39.3%)	<0.001
MRA	3535 (53.3%)	2343 (23.2%)	<0.001
CCB	2013 (30.3%)	5649 (56.0%)	<0.001
Beta-blocker	4464 (67.3%)	5167 (51.2%)	<0.001
ACEI/ARB/ARNI	4533 (68.3%)	5673 (56.2%)	<0.001
Statin	4891 (73.7%)	6380 (63.3%)	<0.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; CCB, calcium channel blockers; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LAD, left atrial diameter; LVSD, left ventricular end-systolic diameter; LVDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist.
[a]Estimated glomerular filtration rate <60 mL/min/1.73 m^2.

(1707 patients) in the non-HF group received a cancer diagnosis at an average age of 71.2 ± 10.4 years. The mean duration of follow-up was 5.2 ± 3.0 years, ranging from 1 to 14 years. The median period from HF to cancer diagnosis was 3.5 years (IQR: 1.8–5.9 years). *Table* 3 shows the correlation between HF diagnosis and the total cancer incidence in the multivariate-adjusted model (HR 1.58, 95% CI 1.48–1.69). The above analysis was repeated using no HF as a reference in HFpEF and HFrEF cohorts. Both HFpEF (HR 1.69, 95% CI, 1.57–1.81; $P < 0.001$), and HFrEF (HR 1.32, 95% CI 1.20–1.46; $P < 0.001$) were found to be significantly linked to a higher incidence of total cancer. Kaplan–Meier curves for survival free from cancer stratified by HF status are shown in *Figure* 1.

The link between HF status and site-specific cancers was demonstrated in *Table* 3, indicating associations with obesity-related cancer (HR 1.68, 95% CI 1.52–1.86), tobacco-related (HR 1.62, 95% CI 1.47–1.78), lung cancer (HR 1.55, 95% CI 1.34–1.79), colorectal cancer (HR 1.86, 95% CI 1.56–2.21) and breast cancer (HR 1.44, 95% CI 1.04–1.98). HFpEF had a substantial association with the occurrence of all site-specific cancers. HFrEF had a moderate association with the event of most cancers but no significant differences in breast cancers (HR 1.26, 95% CI 0.74–2.16; P = 0.394). Kaplan–Meier curves for survival free from site-specific cancers are shown in *Figure* 2.

Association between HF status and incidence of cancer in males and females

Table 4 presents the link between HF status and the incidence of total cancers stratified by males and females. Both women and men with HF had a significant risk of developing incident cancer compared with women and men without HF (HR 1.95, 95% CI 1.74–2.18, $P < 0.001$, for females and HR 1.41, 95% CI 1.30–1.54, $P < 0.001$, for males). Additionally, when compared with non-HF individuals, both HFpEF and HFrEF women showed an increase in cancer risk (HR 2.03, 95% CI 1.81–2.28, $P < 0.001$, for HFpEF vs. HR 1.44, 95% CI 1.19–1.74, $P < 0.001$, for HFrEF). The overall cancer risk was also significantly increased in men with either HFpEF or HFrEF (HR 1.49, 95% CI 1.36–1.64, $P < 0.001$, for HFpEF and HR 1.28, 95% CI 1.14–1.44, $P < 0.001$, for HFrEF).

The increased risk of incident site-specific cancer in males and females HF patients was presented in *Figure* 3 and *Table* 4, including obesity-related cancers (HR 1.90, 95% CI 1.61–2.24, in females and HR 1.56, 95% CI 1.37–1.78 in males), and tobacco-related cancers (HR 2.03, 95% CI 1.71–2.42 in females and HR 1.48, 95% CI 1.32–1.65, in males). HF in each gender was also associated with an excess risk of lung cancer (HR 1.96, 95% CI 1.47–2.61, in females and HR 1.43, 95% CI 1.21–1.69, in males) and colorectal cancer (HR 2.98, 95% CI 2.10–4.24, in females and HR 1.58, 95% CI 1.29–1.94, in males). In contrast, the risk of breast cancer did not differ between HF status and control subjects over the whole HF status (all $P > 0.05$). Kaplan–Meier curves for survival free from cancer stratified by gender are shown in *Figure* 3. In the forest plots, the connections between HF and the development of cancer are depicted (*Figure* 4). Our study and the one conducted by Leedy et al. are the only ones reporting the correlation between HF and incident cancer based on HF phenotypes. There are consistent findings regarding the association between HFpEF and the incidence of cancer, whereas the results are inconsistent for HFrEF. Overall, the combined results suggest a non-significant, inverse association between the use of statins and steatosis for any HF (pooled HR: 1.61, 95% CI 1.33–1.95).

Discussion

In our current Chinese cohort study, we explored the relationship between HF and the development of cancer. Our

Table 3 Association of HF status with incident total and site-specific cancers.

		Age and sex adjusted		Multivariable adjusted[a]	
	No. of events	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Any cancer	4240 (12.8%)				
No HF	1707 (10.5%)	1.0 (reference)		1.0 (reference)	
Any HF	2533 (15.1%)	1.39 (1.31–1.48)	<0.001	1.58 (1.48–1.69)	<0.001
HFrEF	689 (10.4%)	1.11 (1.01–1.21)	0.026	1.32 (1.20–1.46)	<0.001
HFpEF	1844 (18.3%)	1.57 (1.47–1.68)	<0.001	1.69 (1.57–1.81)	<0.001
Obesity-related	1836 (5.6%)				
No HF	704 (4.3%)	1.0 (reference)		1.0 (reference)	
Any HF	1132 (6.8%)	1.48 (1.34–1.63)	<0.001	1.68 (1.52–1.86)	<0.001
HFrEF	296 (4.5%)	1.16 (1.01–1.33)	0.031	1.40 (1.20–1.62)	<0.001
HFpEF	836 (8.3%)	1.66 (1.50–1.84)	<0.001	1.79 (1.61–2.00)	<0.001
Tobacco-related	2084 (6.3%)				
No HF	841 (5.2%)	1.0 (reference)		1.0 (reference)	
Any HF	1243 (7.4%)	1.43 (1.31–1.56)	<0.001	1.62 (1.47–1.78)	<0.001
HFrEF	363 (5.5%)	1.17 (1.04–1.33)	0.012	1.39 (1.22–1.60)	<0.001
HFpEF	880 (8.7%)	1.59 (1.44–1.76)	<0.001	1.72 (1.55–1.90)	<0.001
Lung	892 (2.7%)				
No HF	375 (2.3%)	1.0 (reference)		1.0 (reference)	
Any HF	517 (3.1%)	1.36 (1.19–1.55)	<0.001	1.55 (1.34–1.79)	<0.001
HFrEF	163 (2.5%)	1.17 (0.97–1.40)	0.103	1.38 (1.13–1.70)	0.002
HFpEF	354 (3.5%)	1.48 (1.28–1.72)	<0.001	1.62 (1.39–1.89)	<0.001
Colorectal	631 (1.9%)				
No HF	231 (1.4%)	1.0 (reference)		1.0 (reference)	
Any HF	400 (2.4%)	1.61 (1.37–1.90)	<0.001	1.86 (1.56–2.21)	<0.001
HFrEF	113 (1.7%)	1.29 (1.03–1.62)	0.027	1.62 (1.26–2.07)	<0.001
HFpEF	287 (2.8%)	1.82 (1.52–2.18)	<0.001	1.96 (1.63–2.35)	<0.001
Breast	185 (0.6%)				
No HF	69 (0.4%)	1.0 (reference)		1.0 (reference)	
Any HF	116 (0.7%)	1.16 (0.86–1.56)	0.336	1.44 (1.04–1.98)	0.027
HFrEF	20 (0.3%)	0.91 (0.55–1.50)	0.719	1.26 (0.74–2.16)	0.394
HFpEF	96 (1%)	1.23 (0.90–1.68)	0.193	1.47 (1.06–2.04)	0.022

Abbreviations: HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.
[a]Adjusted for age, sex, body mass index, current smoking, current drinking, hypertension, diabetes mellitus, myocardial infarction, atrial fibrillation, previous stroke and chronic kidney disease.

findings indicate that HF is associated with an elevated risk of cancer incidence. Furthermore, we investigated whether this association varied depending on the HF phenotype. We observed that both HFpEF and HFrEF were linked to an increased risk of developing cancer, with HFpEF showing a potentially higher risk compared with HFrEF. This heightened risk was consistent across various cancer types and remained statistically significant irrespective of gender.

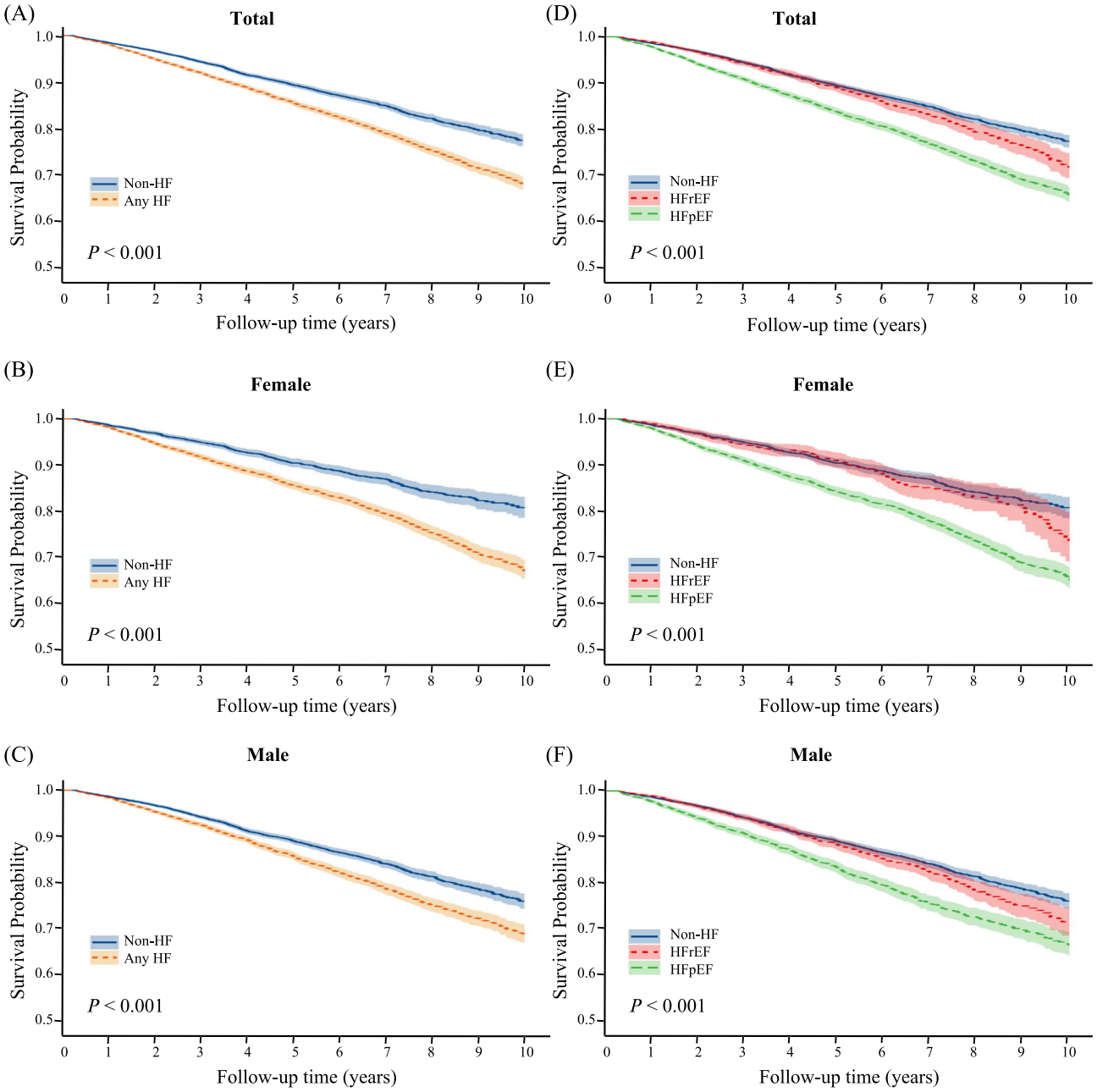
HF is associated with an increased risk of incident cancer

HF is associated with an increased risk of developing cancer, with estimated incidence rates ranging from 18.9 to 33.7 per 1000 person-years.[11–13,16,17] This aligns with previous evidence highlighting elevated cancer risk among HF patients. For instance, Hasin et al. reported in a survey involving 961 HF patients diagnosed by Framingham criteria, that these individuals had a 68% higher likelihood of developing cancer compared with age-, sex- and date-matched community controls, even after adjusting for factors like body mass index and smoking.[11] Similar findings have been observed across specific HF populations, such as those with chronic HF or post-myocardial infarction HF, when compared with the general population.[12,13] In Germany, Roderburg et al. found that outpatients with HF had a significantly higher incidence of cancer (HR 1.76, 95% CI: 1.71–1.81), reinforcing the association between HF and increased cancer risk.[16] Similarly, research conducted within the Italian healthcare system documented higher rates of both cancer incidence and cancer-related mortality among HF patients compared with non-HF control subjects.[17]

Association between HF and cancer: Is gender the answer?

Conflicting findings regarding incident cancer risk in patients with HF have emerged, especially from the PHS and the WHI study.[11–19] The PHS, focusing exclusively on male physicians aged 40 years or older, utilized self-reported HF based on Framingham criteria, potentially underestimating HF incidence, particularly milder cases.[18] Moreover, the study's cohort was comprised solely of physicians whose baseline characteristics differed from the general population, with a relatively lower prevalence of risk factors. Conversely, the WHI study, involving post-menopausal women

Figure 1 Kaplan–Meier curves for survival free from cancer in different HF status. Abbreviations: HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.



aged 50 years or older, found an increased cancer risk associated with HF.[19] However, due to its exclusive focus on women and reliance on hospitalization records for HF diagnosis, there may have been an overestimation of HF incidence among patients with severe symptoms. Furthermore, the WHI study's findings were partly influenced by prior clinical trials on hormone replacement therapy, which could have introduced confounding factors. Both studies were observational cohorts, making it challenging to establish causality due to potential confounding variables. In our current study, we observed that both male and female HF patients have a higher incidence of cancer compared with those without HF. Notably, women with HF exhibited a relatively higher risk of incident cancer compared with men (HR 1.95, 95% CI 1.74–2.18, vs. HR 1.41, 95% CI 1.30–1.54). Among HF patients, the risk of cancer in men did not significantly differ between HFpEF and HFrEF phenotypes. In contrast, women with HFpEF showed a greater

Figure 2 Kaplan–Meier curves for survival free from site-specific cancers in different HF status stratified by gender. Abbreviations: HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

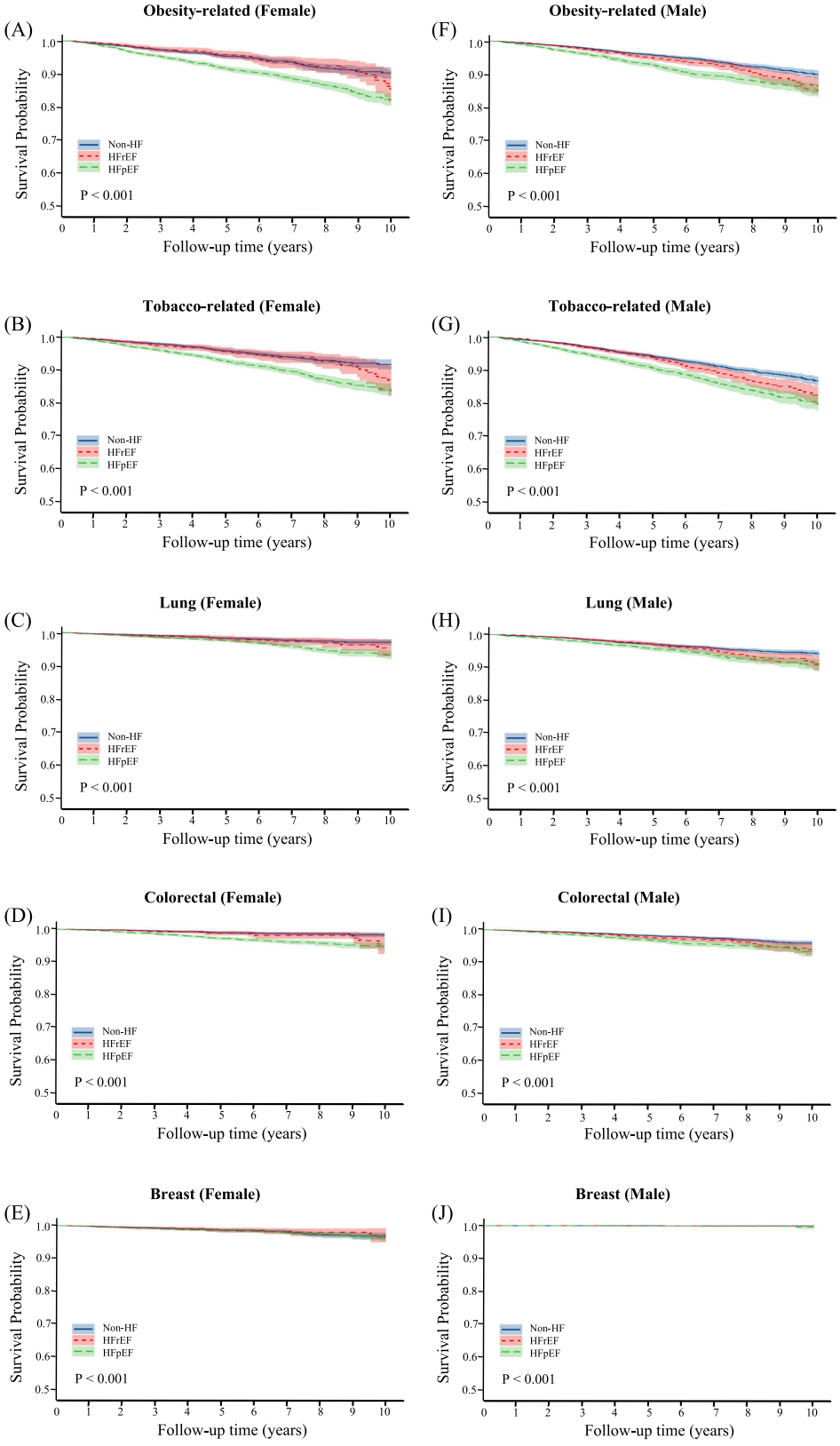


Table 4 Association of HF status with incident total and site-specific cancers stratified by genders.

	Female			Male		
	No. of events	HR (95% CI)[a]	*P* value	No. of events	HR (95% CI)[a]	*P* value
Any cancer	1676(13.1%)			2564 (12.7%)		
No HF	473 (9%)	1.0 (reference)		1234 (11.2%)	1.0 (reference)	
Any HF	1203 (16%)	1.95 (1.74–2.18)	<0.001	1330 (14.5%)	1.41 (1.30–1.54)	<0.001
HFrEF	163 (9.2%)	1.44 (1.19–1.74)	<0.001	526 (10.8%)	1.28 (1.14–1.44)	<0.001
HFpEF	1040 (18.1%)	2.03 (1.81–2.28)	<0.001	804 (18.6%)	1.49 (1.36–1.64)	<0.001
Obesity-related	813 (6.4%)			1023 (5.1%)		
No HF	233 (4.4%)	1.0 (reference)		471 (4.3%)	1.0 (reference)	
Any HF	580 (7.7%)	1.90 (1.61–2.24)	<0.001	552 (6%)	1.56 (1.37–1.78)	<0.001
HFrEF	75 (4.2%)	1.30 (0.98–1.73)	0.064	221 (4.6%)	1.42 (1.19–1.70)	<0.001
HFpEF	505 (8.8%)	2.00 (1.69–2.35)	<0.001	331 (7.6%)	1.64 (1.41–1.89)	<0.001
Tobacco-related	714 (5.6%)			1370 (6.8%)		
No HF	197 (3.7%)	1.0 (reference)		644 (5.8%)	1.0 (reference)	
Any HF	517 (6.9%)	2.03 (1.71–2.42)	<0.001	726 (7.9%)	1.48 (1.32–1.65)	<0.001
HFrEF	70 (3.9%)	1.51 (1.13–2.03)	0.006	293 (6%)	1.36 (1.17–1.59)	<0.001
HFpEF	447 (7.8%)	2.11 (1.77–2.52)	<0.001	433 (10%)	1.54 (1.36–1.75)	<0.001
Lung	265 (2.1%)			627 (3.1%)		
No HF	74 (1.4%)	1.0 (reference)		301 (2.7%)	1.0 (reference)	
Any HF	191 (2.5%)	1.96 (1.47–2.61)	<0.001	326 (3.5%)	1.43 (1.21–1.69)	<0.001
HFrEF	28 (1.6%)	1.62 (1.01–2.60)	0.045	135 (2.8%)	1.34 (1.07–1.68)	0.01
HFpEF	163 (2.8%)	2.01 (1.51–2.69)	<0.001	191 (4.4%)	1.48 (1.23–1.79)	<0.001
Colorectal	212 (1.7%)			419 (2.1%)		
No HF	43 (0.8%)	1.0 (reference)		188 (1.7%)	1.0 (reference)	
Any HF	169 (2.2%)	2.98 (2.10–4.24)	<0.001	231 (2.5%)	1.58 (1.29–1.94)	<0.001
HFrEF	19 (1.1%)	1.92 (1.08–3.44)	0.027	94 (1.9%)	1.55 (1.18–2.03)	0.002
HFpEF	150 (2.6%)	3.13 (2.20–4.46)	<0.001	137 (3.2%)	1.60 (1.28–2.01)	<0.001
Breast	177 (1.4%)			8 (0.0%)		
No HF	66 (1.3%)	1.0 (reference)		3 (0.0%)	1.0 (reference)	
Any HF	111 (1.5%)	1.37 (0.98–1.90)	0.063	5 (0.1%)	3.49 (0.77–15.76)	0.104
HFrEF	19 (1.1%)	1.23 (0.71–2.13)	0.469	1 (0.0%)	1.89 (0.16–22.44)	0.613
HFpEF	92 (1.6%)	1.39 (0.99–1.95)	0.054	4 (0.1%)	4.12 (0.87–19.46)	0.074

Abbreviations: HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.
[a]Adjusted for age, sex, body mass index, current smoking, current drinking, hypertension, diabetes mellitus, myocardial infarction, atrial fibrillation, previous stroke and chronic kidney disease.

cancer risk compared with those with HFrEF. These findings highlight gender-specific differences in cancer risk associated with HF phenotypes.

HF phenotype and incident cancer risk

In the current study, over a 4.6-year (IQR: 2.6–7.3 years) period, it was found that 15.1% of individuals in the HF group developed cancer (at an average age of 71.9 years). The median time between HF and cancer diagnoses was 3.5 years (IQR: 1.8–5.9 years). We investigated if this association was dependent on HF phenotype. Both HF phenotypes were associated with a significant risk of cancer. The risk was greater in HFpEF compared with HFrEF patients (HR 1.69, 95% CI, 1.57–1.81, $P < 0.001$, and HR 1.32, 95% CI 1.20–1.46; $P < 0.001$, respectively). Most previous studies did not assess the HF phenotype on the risk of incident cancer. In a sub-cohort of the WHI study, when available data from 41 503 post-menopausal women existed, HFpEF was significantly associated with cancer risk (HR 1.34, 95% CI 1.06–1.67) while HFrEF was not (HR 0.99, 95% CI 0.74–1.34). The authors highlighted the importance of further investigating this relationship, including male patients.[19]

Potential mechanisms between HF and cancers

In our study, both HFpEF and HFrEF were associated with an increased risk of subsequent cancer, with HFpEF showing a potentially greater risk. Previous research has proposed two main mechanisms to explain this association.[24–28] The first suggests a shared pathological environment characterized by chronic inflammation and oxidative stress, common features in both HF and cancer.[29,30] The second mechanism highlights the sustained activation of the sympathetic nervous system, renin–angiotensin–aldosterone system and natriuretic peptides axes, which are prominent in HF progression and may contribute to cancer development.[31] Our findings revealed a significant association between HF and cancer even after accounting for traditional cardiovascular risk factors such as hypertension, diabetes mellitus and myocardial infarction. This suggests the existence of additional unmeasured risk factors could contribute to both conditions rather than one condition directly causing the other. While HFpEF and HFrEF result from distinct pathophysiological mecha-

Figure 3 Association of HF status with incident total and site-specific cancers stratified by gender. Abbreviations: HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

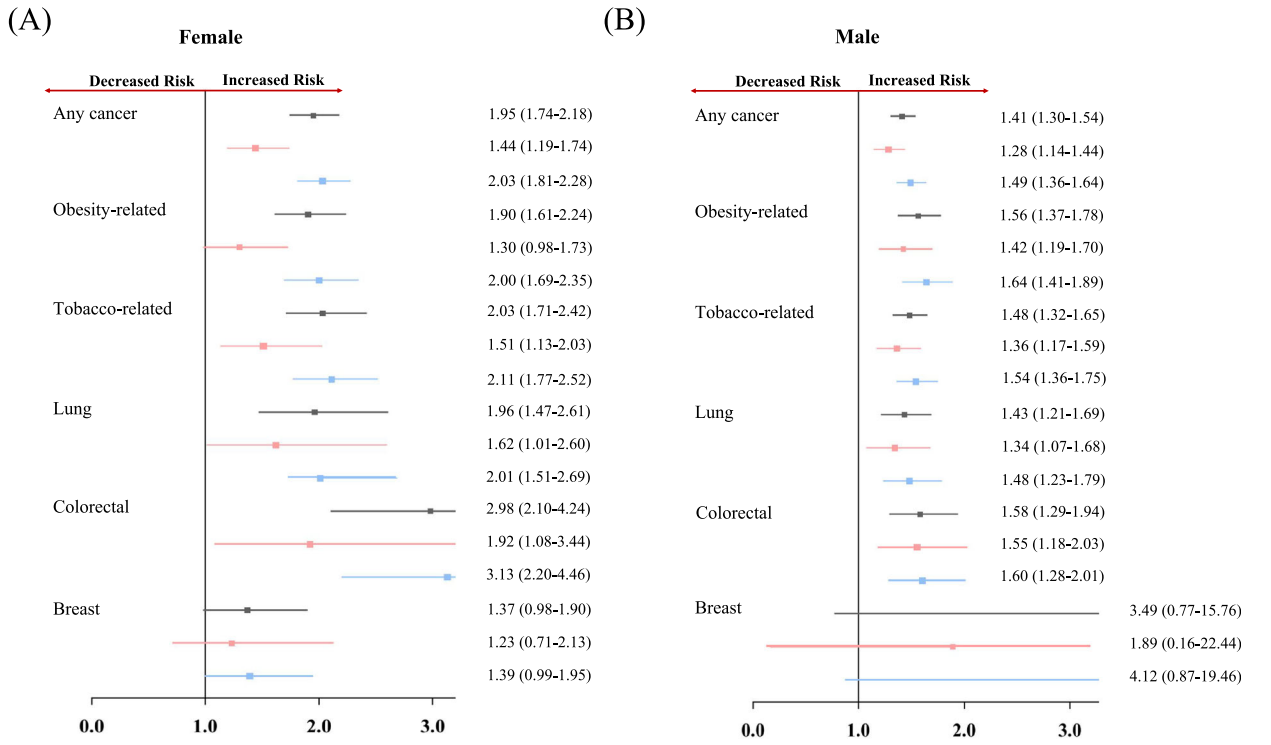
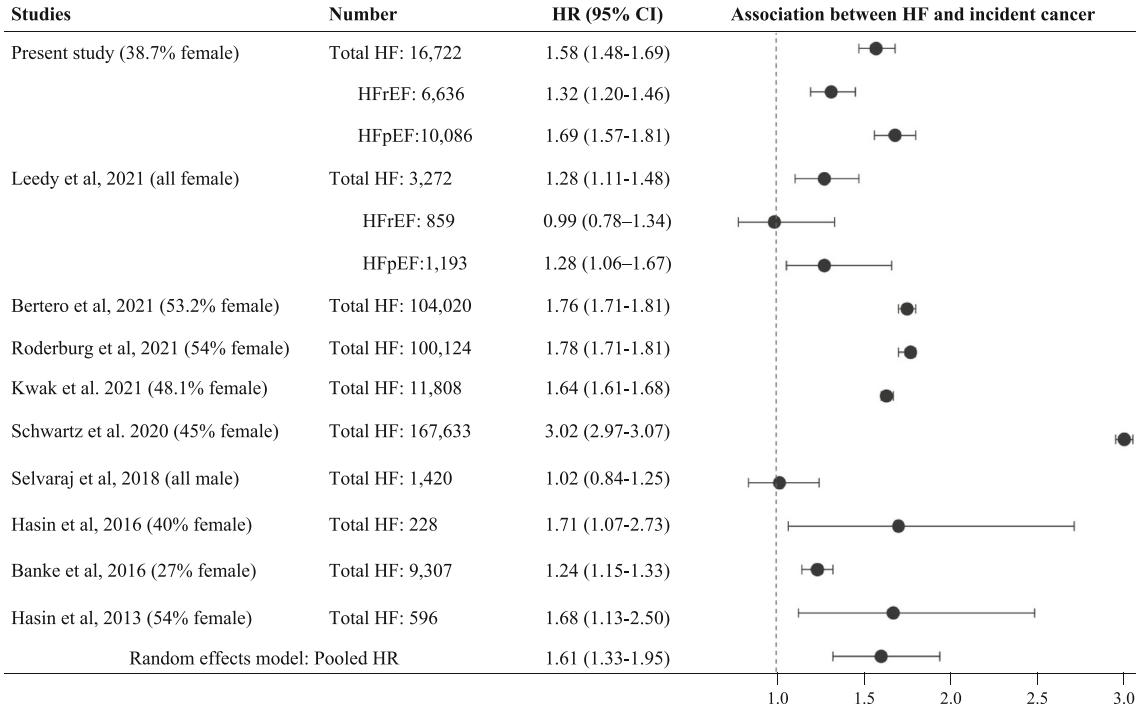


Figure 4 Forest plots showing the association of HF with incident cancer. Abbreviations: HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.



nisms rather than representing different stages of HF progression, these shared risk factors may be integral to the clinical syndrome of HF.[32,33] The stronger association of pathophysiological pathways and cardiometabolic factors involving oxidative stress, neuro-hormonal activation and chronic inflammation with HFpEF compared with HFrEF may explain the potentially higher risk of cancer observed in HFpEF patients. These insights underscore the complex interplay between HF and cancer, warranting further investigation into shared etiological pathways and targeted preventive strategies.

Study limitations

We acknowledge several limitations in our study. First, its observational nature inherently poses challenges in fully mitigating residual confounding factors despite our efforts to adjust for known variables. Second, the incidence of cancer may have been underestimated because our study relied on electronic medical records from our institution, potentially missing cases treated elsewhere. Third, despite a sizable cohort of over 30 000 adults with echocardiograms at baseline, our ability to detect small to moderate associations in HFrEF may have been limited, possibly explaining previous studies' lack of association between HFrEF and cancer (or specific types of cancer). Fourth, we did not present data on HF with mildly reduced EF (HFmrEF). Because this category often overlaps with two other phenotypes (HFmrEF may be the result of the improvement of HFrEF or the deterioration of HFpEF). Therefore, it is quite difficult to draw reliable and definite conclusions about the risk of cancer incidence in HFmrEF patients. Moreover, HFmrEF accounts for 10%–20% of HF patients, and a longer follow-up period might be needed to reveal statistically significant differences among these HF phenotypes. Lastly, we cannot discount the possibility of heightened medical care and cancer surveillance among HF survivors, potentially skewing our findings towards increased cancer detection.

Conclusions

Individuals with HF exhibited a higher incidence of cancer compared with those without HF. This elevated risk of incident cancer was observed in both HFpEF and HFrEF, with a potentially greater risk noted in HFpEF. The excess risk is applied to both males and females, as well as virtually most types of cancer. Importantly, this excess risk spanned across genders and encompassed most types of cancer. These findings carry significant implications for the management and care of HF patients, highlighting the need for further research to elucidate the mechanisms linking HF and cancer incidence.

Conflict of interest statement

All authors have no conflicts of interest.

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Data availability statement

The data that support the findings of this study are available from the corresponding author (zhouxiaodong@wmu.edu.cn) upon reasonable request.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supporting Information.

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